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Pharmacokinetics of omeprazole and its metabolites in premenopausal and postmenopausal females

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The pharmacokinetic (PK) of omeprazole (OMP), 5-hydroxy-omeprazole (5-OH-OMP) and omeprazole sulphone (OMP-SUL), was investigated in healthy premenopausal and postmenopausal females. A single oral dose, open-label, non-controlled, pharmacokinetic study was conducted in healthy premenopausal (n = 16) and postmenopausal (n = 8) females. The samples were analyzed using reversed phase high performance liquid chromatography (HPLC), different pharmacokinetics (PK) parameters were determined and compared statistically to evaluate the difference between two groups. The activities of CYP2C19 and CYP3A4 were determined as $AUC_{OMP}/AUC_{OH\text{-}OMP}$ and $AUC_{OMP}/AUC_{OMP\text{-}SUL}$, respectively. The significant differences ($P < 0.05$) between C_{max}, t_{max}, $[AUC]_0^t$, $[AUC]_0^\infty$, $t_{1/2}$ and metabolic ratios (MR) of OMP, 5-OH-OMP and OMP-SUL were observed between premenopausal and postmenopausal females. The present studies showed the higher AUC and longer $t_{1/2}$ in postmenopausal subjects. The increase in MR for 5–OH-OMP and also OMP-SUL determined as $AUC_{OH\text{-}OMP}/AUC_{OMP}$ and $AUC_{OMP\text{-}SUL}/AUC_{OMP}$, respectively, was also observed in postmenopausal females compared with the premenopausal females.

Key words: Omeprazole, pharmacokinetics, menopause.

INTRODUCTION

The perimenopause and menopause are associated with manifestation of hyperacidity, along with hot flashes (Pachman et al., 2012; Machowska et al., 2004), depression and insomnia (Cuadros et al., 2012; Freeman et al., 2007). Postmenopausal females have higher propensity for gastric hyperacidity (Machowska et al., 2004), which is associated with increased use of gastric antisecretary drugs including proton pump inhibitors (PPIs). The increased risk of hip bone fracture has been reported in postmenopausal females, accompanied with the use of OMP (Roux et al., 2009). Menopause is associated with hormonal transitions (Davison et al., 2005), which affects metabolism of drugs (Simpson and Davis, 2001) and this may lead to altered pharmacokinetics (PK) in postmenopausal females.

The OMP is metabolized in the liver by CYP2C19 to 5-OH-OMP (70%) (Andersson et al., 1994; Karam et al., 1996; Cederberg et al., 1989) and by CYP3A4 into OMP-SUL (30%) and a major secondary metabolite is hydroxyl sulphone (OH-SUL) obtained from 5-OH-OMP and OMP-SUL (Andersson et al., 2012).

PK of OMP has been accomplished considering genetic polymorphism (Andersson, 1990; Ramsjö, 2010) racial or interethnic differences (Kim et al., 2004; Ieiri et al., 1996), and population PK (Gonzalez et al., 2003; Chang et al., 1995), but in these studies PK were evaluated without

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Table 1. Demographic characters of pre and postmenopausal subjects.

Group	Pre (n=16)	Post (n=8)
Age (years)	24.0±0.30	55.90±0.74*
Weight (kg)	52.60±2.13	66.50±2.04
Height (cm)	148±3.2	150.40±5.1
BMI	24.5±0.43	29.6±0.52

*Significant at P<0.05; NS, Non significant; Pre, premenopausal females; Post, postmenopausal females; BMI, body mass index. Demographic characters have been shown

considering genders differences or menopausal status of females. Though, PK profile of OMP has been investigated in males; however, in females it is obscure, including the postmenopausal females and this needs further exploration (Sakai et al., 2001). Different variables, which may affect PK and clinical outcome of drugs, must be investigated in order to optimize the dose regimen (Weston and Hood, 2004).

The relationship between the CYP2C19 genotype and PK of OMP in elderly people was established; however, menopause or gender difference was not considered as a potential factor (Ishizawa et al., 2005). The extensive literature survey reveals that available data on the subject of PK of OMP is not sufficient to explain or predict PK of OMP in postmenopausal females.

This study was conducted to investigate the PK differences for OMP and its metabolites 5-OH-OMP and OMP-SUL, as well as to determine the differences of activities of CYP2C19 and CYP3A4 between premenopausal and postmenopausal female.

MATERIALS AND METHODS

An optimized and validated high performance liquid chromatography-ultraviolet (HPLC-UV) method was used for quantitative analysis of OMP, 5-OH-OMP and OMP-SUL (Ahmad et al., 2011). The applied method was validated by determining accuracy, precision, sensitivity and specificity (validation parameters are shown in Table 3 and Table 6). A HPLC system of Perkin Elmer Series 200 (Norwalk, USA), operational with online vacuum degasser, Perkin Elmer Series 200, column oven, and UV-VIS detector were used. Total-chrome workstation software (version 6.3.1) was linked with the LC system by network chromatography interface (NCI) 900.

OMP, 5-OH-OMP, OMP-SUL and pantoprazole, used as internal standard (IS), were provided by Astra Zeneca (Sweden) and Medicraft (Pvt.) Ltd. (Peshawar, Pakistan), respectively. HPLC grade methanol, potassium dehydrogenate phosphate and sodium hydroxide (NaOH) were purchased from Sigma-Aldrich (oslo, Norway), Fischer Scientific (Leicestershire, UK) and Merck (Darmstadt, Germany), respectively. Distilled water prepared by Millipore (Milford, USA) distillation apparatus was used throughout this study.

Study design

A single dose, open-label, non-controlled, premenopausal and postmenopausal cohort PK study was designed to investigate the PK of OMP and the activities of CYP2C19 and CYP3A4 in premenopausal (n = 16) and postmenopausal (n = 8) healthy female volunteers. This study was conducted in agreement with the principles of international conference on harmonization for conducting good clinical practice and declaration of Helsinki. This study was approved by ethical committee of Department of Pharmacy, University of Peshawar. Application number 13/EC/Pharm.ref number 12/Pharm.

Selection of volunteers

Healthy premenopausal (n = 16) and postmenopausal (n = 8) females were selected. The design and purpose of the study was explained to volunteers and a written informed consent was obtained. The mean ± standard deviation (SD) age of the premenopausal volunteers was 24.0 ± 0.23 years and for postmenopausal females, it was 55.90 ± 0.74 years. The body weights of premenopausal and postmenopausal female volunteers were 52.60 ± 2.13 and 66.50 ± 2.04 kg, respectively. All premenopausal female subjects had a regular menstrual cycle of 28 days. The postmenopausal females had entered the menopause completely for minimum one year passed after the cessation of their last menstrual cycle. The overall health status of postmenopausal females was satisfactory, free of any gross level pathological evidence, but fluctuation in their blood pressures was compromised. The demographic data of volunteers is shown in Table 1. Prior to inclusion of volunteers in the experiment, complete medical histories were obtained and full body screening by various laboratory tests was performed like blood hemoglobin, serum cholesterol, serum bilirubin, serum creatinine, low density lipoprotein (LDL)-cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, very low density lipoprotein (VLDL)-cholesterol to determine their health status. The clinical data is shown in Table 2.

Drug administration and blood sampling

The subjects were instructed to avoid intake of any medication including herbal medicines a week before the study. The volunteers were kept on overnight fasting before trial, no juice, caffeine or food intake was allowed except water before studies. At about 8.00 AM, each volunteer received OMP capsules (40 mg) with a full glass of water (ca ≈ 250 ml). The blood samples (≈ 5 ml) were collected from cubital vein and occasionally collected from cephalic vein, at 0.0, 0.5, 1.0, 2, 3, 4, 6 and 8 h. The blood samples were centrifuged and the plasma was separately stored at -80°C till analysis. The standard breakfast and lunch was served after 3 and 5 h, respectively, following the drug administration.

Standard solutions

Stock solutions (1 mg/ml) of OMP, 5-OH-OMP and OMP-SUL were prepared by dissolving the drug and metabolites in methanol. Working solutions were prepared by diluting the stock solution in Eppendorf tubes (2 ml) in the concentration ranges of 5 to 500 ng/ml for each OMP and OMP-SUL, while 10 to 1000 ng/ml for 5-OH-OMP, respectively. The concentration of internal standard (IS) (1 µg/ml) was kept constant in all dilutions. While preparing plasma sample, plasma (150 µl) and 50 µl of each of analyte and internal standard were taken (Ahmad et al., 2011).

Sample preparation

Plasma sample thawed at room temperature and sample (150 µl) were transferred to Eppendorf tube. Then pantoprazole, used as an

Table 2. Clinical data of pre and postmenopausal female participants of pharmacokinetic study of OMP and its metabolites.

Clinical value	Unit	Pre (n=16)	Post (n=16)	P value
Hb	gm/dl	14.44±0.23	12.84±0.32	0.0014**
Serum bilirubin	mg/dl	0.56±0.3	0.77±0.5	0.0021**
Serum creatinine	mg/dl	0.66±0.05	0.8±0.05	0.1142
Serum cholestrol	mg/dl	133.8±8.5	144.2±4.2	0.3
Serum triglyceride	mg/dl	84.63±10.32	114.0±7.8	0.04*
HDL cholesterol	mg/dl	31.25±4.4	81.13±4.4	0.2
LDL cholesterol	mg/dl	71.88±5.3	78.5±4.3	0.84

*Significant at P<0.05, **Significant at P<0.005, ***Significant at P<0.0005, Hb, hemoglobin value; HDL cholesterol, high density lipid cholesterol; LDL cholesterol, Low density lipid cholesterol.

Table 3. Pharmacokinetic parameters of OMP (40 mg) following oral administration in pre and postmenopausal female volunteers.

PK	Unit	OMP		P-value	95% confidence interval
		Pre (n=16)	post (n=8)		
C_{max}	µg/ml	2.9±0.60	3.7±0.50	0.003**	-1.4 to -0.34
t_{max}	h	2.3±0.2	2.583±0.4	0.14	-0.60 to 0.10
$[AUC]_0^t$	µg.h/ml	8.7±2.24	15.3±2.24*	0.0001***	-12.81to -7.62
$[AUC]_0^\infty$	µg.h/ml	9.7±3.31	19.38±2.9*	0.0001***	-18.8 to -0.6
Vd	ml/kg	315.4±97.9	469.3±125.1	0.011*	-265.5 to -42.3
CL	ml/h/kg	111.6±20.69	58.40±8.62*	0.0001***	40.5 to 65.5
$t_{1/2}$	h	2.3±0.8	2.9±0.24	0.01*	-1.06 to -0.2

*significant at $p < 0.05$, ** significant at $p < 0.005$, ***significant at $p < 0.0005$; PKs , pharmacokinetic parameters, compared in pre and postmenopausal females for OMP ;Cmax, maximum plasma concentration:tmax, time to achieve the maximum plasma concentration;t1/2 ,elimination half life;AUC0-t ,Area under the plasma concentration time curve from 0 time to last sampling time;AUC∞ , Area under the plasma concentration time curve from 0 hr to infinity time,Vd,volume of distribution; CL, clearence of analyte from body

internal standard, was added and vortexed for 30 s. Three parts of methanol (450 µl) was added, vortexed for further 3 min and then centrifuged at 5000 rpm at 0˚C for 5 min. The separated clear layer of plasma was transferred to Eppendorf tube (Ahmad et al., 2011).

Chromatography

Chromatographic separation was achieved using Supelco/discovery C_{18} (150 × 4.6 mm, 5 µm) analytical columns protected by a Perkin Elmer C_{18} (30 × 4.6 mm, 10 µm; Norwalk, USA), pre-column guard cartridge, the temperature of the column was 45°C and the detector wavelength was adjusted at 302 nm. The mobile phase, ratio of methanol and buffered (pH 7.2) aqueous phase of potassium dehydrogenate phosphate (42:58 v/v) were pumped, at the flow rate of 0.8 ml/min. Different optimized parameters are shown in Table 3.

PK analysis

Plasma concentration of OMP, 5-OH-OMP, and OMP-SUL as a function of time was plotted on semi-log scale to evaluate various PK parameters. The data was also analyzed using PK-Solution® 2.0 software for non-compartmental data analysis.

Statistical analysis

The software programme used for statistical analysis was graph pad prism 5 and Statistical Package for Social Sciences (SPSS) 16. The data was presented as mean ± standard deviation (SD) and the difference between various groups was studied using student *t*-test at 95% confidence interval.

RESULTS

PK of OMP and its metabolites

Volunteers characteristics

The demographic and clinical data of the volunteers is shown in Tables 1 and 2, respectively. The age of postmenopausal females was significantly higher when compared with the premenopausal females ($P < 0.05$), while the rest of the demographic characters did not display any significant difference. Hemoglobin value was significantly higher in premenopausal females ($P < 0.005$)

Table 4. Pharmacokinetic parameters of metabolite, 5-OH-OMP following oral administration of OMP (40 mg) in pre and postmenopausal female volunteers.

PK	Unit	5-OH-OMP		P-value	95% CI
		Pre (M)	Post (F)		
C_{max}	µg/ml	1.11±0.2	1.252±0.5	0.02*	-0.60 to 0.4
t_{max}	h	2.62±0.20	3.06±0.34	0.020*	-0. 8to -0.099
$[AUC]_0^t$	µg.h/ml	3.13±0.53	3.90±0.7	0.0001***	-1.41 to -0.15
$[AUC]_0^\infty$	µg.h/ml	3.6±0.73	9.486±2.51*	0.0001***	-7.05 to -4.6
Vd	ml/kg	664.3±110.1	640.1±48.5	0.0001***	43.09 to 91.7
CL	ml/h/kg	271.3±52.30	93.88±19.8 *	0.0001***	146.7 to 208.3
$t_{1/2}$	h	2.3±0.79	7.64±2.7*	0.0001***	-6.8 to -3.8
MR	AUC_{OMP}	2.8± 0.63	3.72± 1.3	0.06	-1.9 to 0.04

*Significant at p < 0.05, ** significant at p < 0.005, ***significant at p < 0.0005, MR: metabolic ratio, pharmacokinetic parameters compared in pre and postmenopausal females for 5-OH-OMP.

Table 5. Pharmacokinetic parameters of metabolite, OMP-SUL following oral administration of OMP (40 mg) in pre and postmenopausal female volunteers.

PKs	Unit	OMP-SUL		P-value	95% CI
		Pre	Post		
C_{max}	µg/ml	0.25±0.032	0.18±0.082	0.012*	0.030 to 0.2
t_{max}	Hr	3.5±0.42	4.040±0.8	0.1069	-1.24 to 0.14
$[AUC]_0^t$	µg.hr/ml	0.75±0.2	0.8±0.2	0.3821	-0.3 to 0.11
$[AUC]_0^\infty$	µg.hr/ml	1.4±0.42	3.653±1.6	0.0062**	-3.63 to -0.9
Vd	ml/kg	5155±1715	5996±2051	0.3383	-2676 to 995.6
CL	ml/hr/kg	1527±610.2	779.7±467.3	0.004**	273.4 to 1223
$t_{1/2}$	Hr	4.06±1.07	26.58±11.9*	0.0001***	-28.89 to -16.17
MR	AUC_{OMP} /$AUC_{OMP-SUL}$	13.08± 6.4	18.16± 6.91	0.08	-10.8 to 0.61

*significant at p < 0.05, ** significant at p < 0.005, ***significant at p < 0.0005, MR: metabolic ratio , pharmacokinetic parameters compared in pre and postmenopausal females for OMP-SUL.

while serum bilirubin (P < 0.005) and serum triglyceride levels (P < 0.05) were significantly higher in postmenopausal females. Rest of the clinical data also did not show any significant difference. Plasma proteins and plasma albumins were insignificantly higher in postmenopausal females.

Gender based PK analysis of omeprazole and its metabolites 5-OH-OMP and OMP-SUL

The plasma OMP, 5-OH-OMP and OMP-SUL concentrations as a function of time are shown in Figures 1, 2 and 3. The PK data of OMP, 5-OH-OMP and OMP-SUL between premenopausal and postmenopausal female were then compared (results are shown in Tables 3, 4 and 5).

In postmenopausal females, 27% increase in C_{max} for OMP (P < 0.005) and 13% increase in t_{max}, (P > *0.05*) compared with the premenopausal females was observed. Also, results in the 75% increase in the $[AUC]_0^t$ and 99% increase in the $[AUC]_0^\infty$ in postmenopausal females (P < 0.0005). The elimination $t_{1/2}$ was also significantly (P < *0.05*) higher (26% higher) in postmenopausal females. The significant increase in volume of distribution (Vd) and decrease in clearance of analyte from body (CL) of OMP was observed in postmenopausal women compared with the premenopausal female volunteers.

The C_{max} and t_{max} of 5-OH-OMP were significantly (P < 0.05) higher in postmenopausal female compared with premenopausal females. The metabolic ratios (MR) exhibited a 32% raise in postmenopausal females. The elimination $t_{1/2}$ value was significantly higher (232% raise) in postmenopausal females, (P < 0.05). Vd and CL increased significantly in premenopausal females.

C_{max} of OMP-SUL decreased upto 28% in postmenopausal

Table 6. HPLC Method validation parameters (Ahmad et al., 2011)

Parameter	Calibration range (mg/mL)	Regression equation	Correlation coefficient	Spiked plasma samples	Regression equation	Correlation coefficient sensitivity	Limit of detection, LOD (ng/mL)	Limit of quantification, LOQ (ng/mL)
OH	0.01–1	Y =1.71 x +0.00	0.999	24.5±0.43	Y = 1.720 x +0.011	0.998	3	10
5-OMP -OMP	0.05—.5	Y = 3.675 x -0.002	0.999	29.6±0.52	Y = 3.581 x -0.05	0.999	1.5	5
OMP-SUL	0.05–.5	Y = 4.430 x -0.00	0.999	0.53	Y = 4.234 x +0.027	0.998	1.3	5

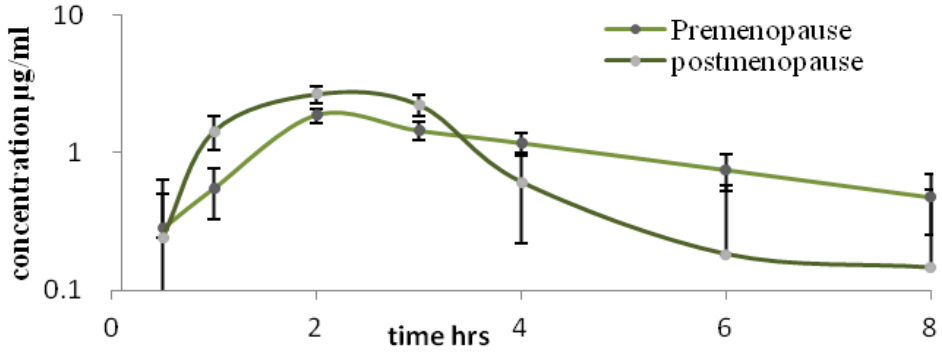

Figure 1. The plasma concentrations of OMP as a function of time in pre and postmenopausal females.

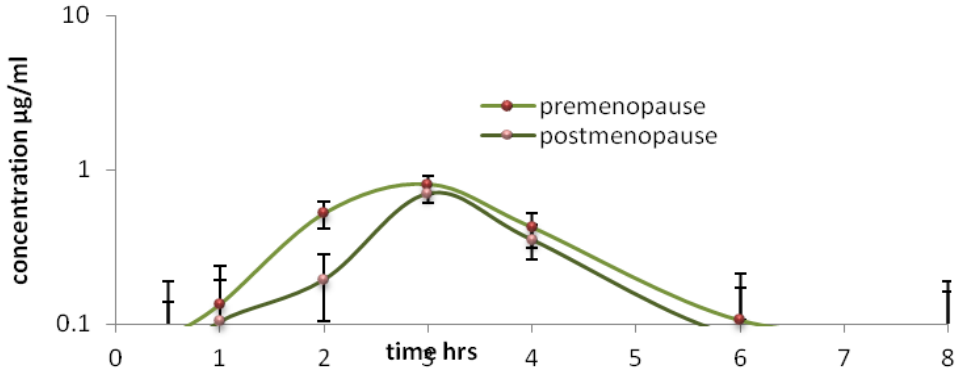

Figure 2. The plasma concentrations of 5-OH-OMP as a function of time in pre and postmenopausal females.

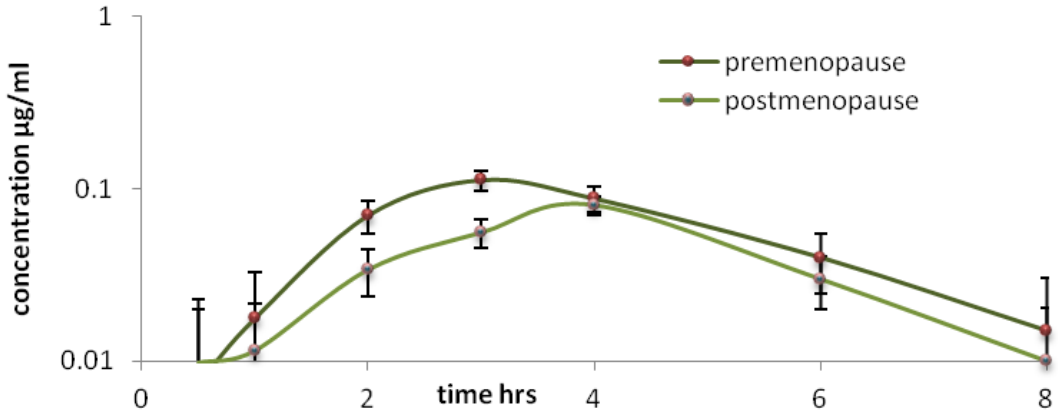

Figure 3. The plasma concentrations of OMP-SUL as a function of time in pre and postmenopausal female.

females compared with premenopausal females ($P < 0.05$) while the t_{max} was 15% higher in postmenopausal females with no significant difference ($P > 0.05$). $[AUC]_0^t$ increased insignificantly ($P > 0.05$) in postmenopausal females compared with premenopausal females. $[AUC]_0^\infty$ showed a significant 163% rise in postmenopausal females. MR was 38% higher in postmenopausal females. $t_{1/2}$ was significantly higher in postmenopausal females. The insignificant increase in Vd in postmenopausal females was observed. CL of OMP-SUL was also significantly higher in premenopausal females compared with the postmenopausal female volunteers.

DISCUSSION

The PK differences of OMP, 5-OH-OMP and OMP-SUL and the activities of CYP2C19 and CYP3A4 in premenopausal and postmenopausal females were determined. Menopause is associated with age therefore the geriatric dose may not be sufficient for the treatment of various ailments in these patients (Schwartz, 2007) and there is need for the adjustment of dose or dosage regimen (Gurwitz et al., 2005). OMP is a highly interactive drug and inhibit various cytochrome P450 enzymes. It is a potent competitive inhibitor of CYP2C19, moderate competitive inhibitor of CYP2C9, very weak competitive inhibitor of CYP2D6 (Ko et al., 1997), and weak non-competitive inhibitor of CYP3A (Tateishi et al., 1995). It has no effect on CYP1A2 or 2E1, but it induces CYP1A1 (Quattrochi and Tukey, 1993). It is possible that OMP may interact with other drugs in multiple drug therapy and PK of the drug may vary in old age, particularly in postmenopausal female. The physiological and biochemical changes that appear in old age are also associated with menopause; like slower gastrointestinal motility (Graff et al., 2008), higher body fat ratio (Carr, 2003) and decreased renal clearance (Christiansen et al., 1971) that may also affect absorption, distribution and clearance of xenobiotics in postmenopausal females.

The C_{max} of OMP in postmenopausal was significantly higher ($P < 0.002$) compared with premenopausal females and the t_{max} slightly increased ($P > 0.14$) in postmenopausal volunteers. Similarly, significant increase ($P<0.0001$) in $[AUC]_0^t$ of the OMP was observed in postmenopausal female compared with the premenopausal volunteers. The AUC in postmenopausal female was increased by 199.78%, that is, revealed by the significantly ($P<0.0001$) higher $[AUC]_0^\infty$ in postmenopausal females. That may be due to the either increase in the absorption of the drug or slower metabolism of the OMP by the postmenopausal female. AUC is determined by gastrointestinal absorption, hepatic metabolism, first-pass effect and volume of distribution. It is known that gastrointestinal motility decreases in postmenopausal females (Graff et al., 2008), that may be the possible reason for increased systemic absorption of OMP. It is also possible that the decrease in the metabolism or decrease in the activities of efflux transporters may increase the systemic exposure of the OMP. The drugs that are substrate of CYP3A4 or P-gp showed higher bioavailability in older females (Krecic-Shepard et al., 2000). OMP is a substrate of P-gp which decreased in old age and may increase the absorption of the OMP. Similarly, the activity of the CYP3A4 also decreased in old age (Krecic-Shepard et al., 2000) and may reduce the metabolism of the drug and results in higher C_{max}. The elimination half-life $t_{1/2}$ was also significantly higher in postmenopausal females, suggesting elimination of OMP is slower in post-menopausal females. The reduced elimination of OMP does not depend on renal clearance/function, as orally administered omeprazole is metabolized completely and 80% is excreted as metabolites in the urine and the remainder 20% is found in the feces, primarily originating from bile secretion.

Therefore, determination of MR plays very important role in evaluating the enzymes activities and metabolites formation which reflect the conversion of OMP into its respective metabolites. MR for both metabolites ($[AUC]_0^\infty$ OMP/$[AUC]_0^\infty$ 5-OH-OMP and $[AUC]_0^\infty$ OMP/$[AUC]_0^\infty$ OMP-SUL, was higher in postmenopausal females when compared with the premenopausal subjects; however, the difference was not significant. Apparently, it suggests that CYP2C19 activity is reduced in postmenopausal females. While the ratio of the metabolites ($[AUC]_0^\infty$ 5-OH-OMP/$[AUC]_0^\infty$ OMP-SUL), increased significantly from 0.389 to 2.6 and may be due to significant decrease in the CYP3A4 activity in the postmenopausal female as it has been observed that the bioavailability of CYP3A4 substrates is higher in such females (Krecic-Shepard et al., 2000).

The Vd was higher while CL of OMP was lower in postmenopausal female when compared with the premenopausal and may be due to the plasma protein binding of the drug as the OMP is the highly protein bound drug (96%). Moreover, the body mass index (BMI) and weight were higher in postmenopausal females and may be a quite plausible reason for higher Vd in postmenopausal females. The change in the protein level may also be responsible for higher concentration of unchanged drug in the postmenopausal volunteers.

The 5-OH-OMP displayed higher values for C_{max}, $[AUC]_0^t$ and $[AUC]_0^\infty$ and t_{max} in postmenopausal females. Previously, no PK study on OMP was conducted, particularly in postmenopausal females but studies in older females suggest that CYP2C19 activity is lower in females (Bachmann and Belloto, 1999). The results of this study support the previous findings. A significantly higher value of $t_{1/2}$ in postmenopausal females was observed. This suggests that CL and Vd of 5-OH-OMP is reduced, as is evident from the higher serum creatinine value of postmenopausal females, indicating reduced glomerular filtration rate (GFR). Aging is associated with decrease in all modes of clearance like glomerular filtration, tubular reabsorption or secretion (Cockcroft and Gault, 1976) and in older females, menopause combined with aging, precipitates decrease in renal clearance (Christiansen et al., 1971).

The OMP-SUL C_{max} and $[AUC]_0^\infty$ displayed a significantly higher value in premenopausal females, though $[AUC]_0^t$ values were not significantly higher. The MR for OMP and OMP-SUL was higher in postmenopausal females suggesting an overall decreased metabolic activity of CYP3A4 in postmenopausal females. The significantly higher value of $t_{1/2}$ in postmenopausal females suggests the same fact that renal CL and Vd were reduced which may be due to increase in the serum creatinine level leading to reduced GFR.

Though, in this study, genetic polymorphism of volunteers was not determined but apparently it is not affecting the status of the results evaluation. The PK studies previously conducted for OMP, neither gender based analysis was performed nor menopause was given any important consideration and the differences between premenopausal and postmenopausal females were not ruled out. Though few studies have been conducted taking OMP as probe drug to determine CYP2C19 and CYP3A4 activities in males and females, but these did not provide most of the information regarding female's PK profile (Laine et al., 2000; Zhang et al., 2006).

Conclusion

The PK differences of OMP and metabolic activities of CYP2C19 and CYP3A4 in premenopausal and postmenopausal female volunteers were evaluated. These findings suggest that postmenopausal females need to be considered as special group of subjects and dose should be adjustment if necessary, particularly in multiple drug therapy where omeprazole exhibits drug interactions.

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ABBREVIATIONS

PK, Pharmacokinetics; **OMP,** omeprazole; **5-OH-OMP,** 5-hydroxy omeprazole; **OMP-SUL**, omeprazole sulphone. IS= Internal standard

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